ADVICES

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Statement on decentralized trials

Decentralized elements are trial related actions that are subcontracted by the sponsor to an external party and not offered via the site.

1. Fully decentralized trials, where there is no contact between the site/PI/treating physician and the patients included in the trial, are **NEVER** acceptable.
2. Decentralization of some trial related actions by sponsors is **NOT ACCEPTABLE** except in some very specific circumstances whereby the sponsor:
   1. Submits an explicit motivation with the trial documents why decentralization is needed for some specific parts of this trial
   2. Motivates how patients would benefit from this decentralization (e.g. video calls via a subcontractor to follow-up on the patient's status …)
   3. Motivates why this decentralization could not be offered by the site
   4. Demonstrates how patient safety (data and physically) is guaranteed
   5. Demonstrates how patient well-being is guaranteed (not being confronted by visits by external people who are not part of the study team)
   6. Demonstrates how GCP standards will be upheld
   7. Guarantees GDPR compliance (and Belgian legislation)

The role of the treating physician, and the patient-physician interaction should be respected.

The participant should always be free in his/her choice to accept the decentralized elements and should be offered equivalent choices. (example, when a patient does not want to be reimbursed for costs via a payment card, they should still be offered the possibility to be reimbursed in via bank transfer)

It should be noted by sponsors that would like to offer decentralized elements, that this would require extra effort from the trial site to handle all the options, sufficient financing of the trial should be taken into account.

The ICF in a trial with decentralized elements should clearly inform the patient about these decentralized elements and offer the participant the option to choose via tick boxes at the end of the ICF. The ICF should also provide all the information on how the subcontractors will handle the personal data of the patient in a clear and understandable way. (for instance: Referring to a link of a privacy policy is not acceptable)

Medical Device Regulation (MDR) : role local EC + timelines EC

If the clinical investigation with a CE-marked medical device, that is used within its intended purpose, is not considered to be a PMCF, only positive advice from the relevant EC(s) is necessary and "Regulatory pathway: EC only" needs to be followed. The "Other clinical investigations" are regulated under the Royal Decree of 18 May 2021 and as such a timeline of 45 days is applicable to issue an EC-decision.

We refer to the pathway in the scheme below:

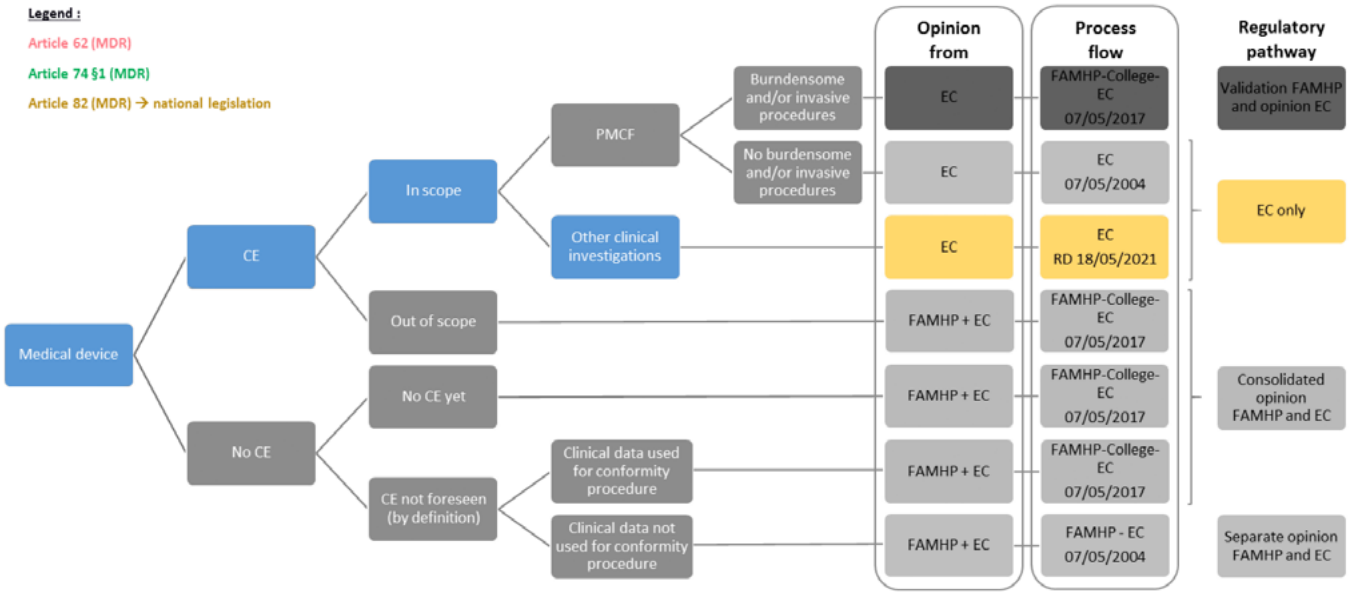


Figure 2. Different regulatory pathways. Different process flows and regulatory pathways are possible depending on the status of the investigational medical device and clinical investigation properties.

Also for Other clinical investigations involving 'in-house' devices or custom-made devices of which data will not be used for conformity assessment, a timeline of 45 days is applicable to issue an EC-decision (Regulatory pathway: Separate opinion FAMHP and EC).

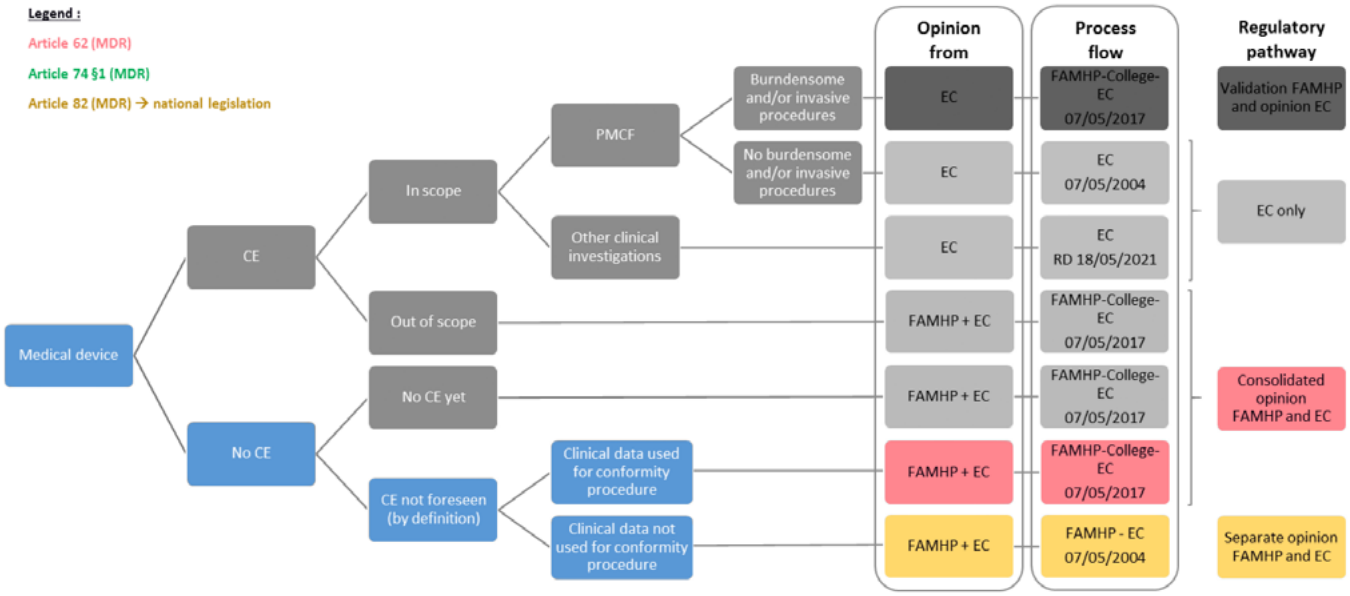


Figure 2. Different regulatory pathways. Different process flows and regulatory pathways are possible depending on the status of the investigational medical device and clinical investigation properties.

In the Royal Decree of 18 May 2021, there is mentioned in article 36 for multicentric studies:

According to **KB 21 May 2021** (medical devices)

T0: Submission at central and local EC
T0: Central EC requests local advice on 1° and 2° (cf. article 36)
T5: Advice of local EC to central EC (accept or decline, except 2°)
T45: Definitive advice to applicant and local EC

When a study falls under the Belgian law on experiments (law of 7 May 2004), a local EC has 25 days to forward an opinion to the Central EC, not 5 days as currently stated in the Royal Decree of 18 May 2021 for other clinical investigations.

We thus see a discrepancy between the law on experiments (law of 7 May 2004) and the Royal Decree of 18 May 2021 regarding the timelines. We also notice a discrepancy in giving advice about the specific documents. A local EC should also consider "the adequacy and completeness of the written information to be provided and the procedure for obtaining consent as well as the justification for research involving persons who are unable to give consent or whose consent cannot be obtained because of the urgency as to their participation in an experiment;"(d.i. 1° Bijlage I, d) 4) and should not only give advice about 2° .

We propose to align the timelines between the different legal texts and to give local ECs 25 days to provide their advice to the central EC, as well as give the local EC the possibility to give advice about the ICF.

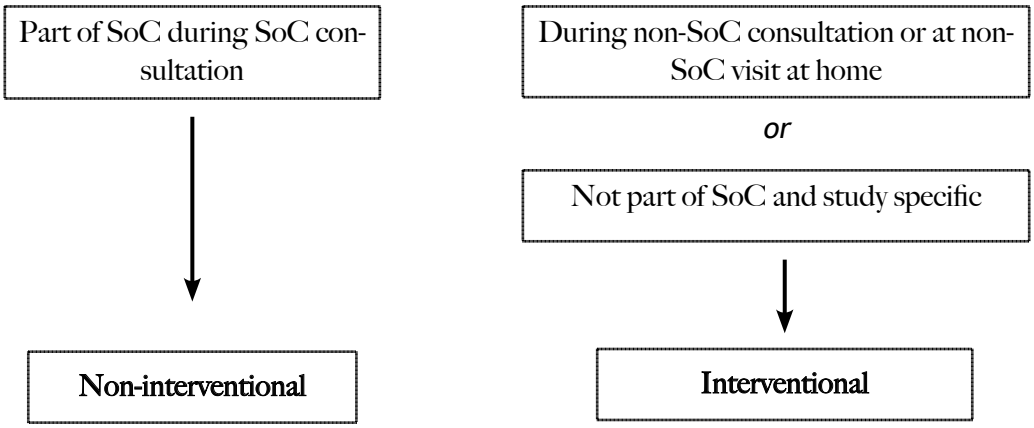
Clinical studies with questionnaire (outside SoC): Interventional vs non-interventional?

From BAREC, we give an advice on how to consider studies involving questionnaires (outside standard of care (SoC)) in order to be considered interventional or non-interventional, in case no additional diagnostic or monitoring procedures are proposed in these studies. Participants will only be requested to complete a questionnaire, and potentially, data can be collected from their medical records.

BAREC wants to highlight that questionnaire completion should not result in longer duration of consultation room occupancy, and should be done at a pre-specified, convenient location with the necessary comfort and privacy for the participant.

The below advice is not applicable to anonymous questionnaires and it is not applicable to quality improvement projects. It is applicable to studies in which the questions are processed pseudonymously and which fall under the (Belgian) law of 7 May 2004.

Please note that interventional studies with questionnaires that also investigate the safety or efficacy of one or more medicinal products, which all have a marketing authorization, are covered by the Clinical Trial Regulation (CTR) and therefore not by the (Belgian) law of 7 May 2004. We refer to the definition of a low-intervention clinical trial according to article 2 (2)(3) of the CTR.



However, EC may ad hoc decide that questionnaire study is considered non-interventional :

- based on content on questions
- if completion of questionnaires requires less than 30 minutes of participant's time
- if questionnaire becomes future part of SoC

ICF template for interventional studies without IMP

We are excited to announce the development of an Informed Consent Form (ICF) template tailored for interventional studies that do not involve medicinal products. This template is specifically designed for interventional studies that do fall under the Law of 7 May 2004 but do not fall under the category of clinical trials (which typically involve medicinal products).

This new ICF template is highly adaptable to a variety of scenarios, such as questionnaire-based studies, research involving additional procedures like blood sampling, scans, tests, comparison of techniques, and other interventions.

You can find the template (in English, French and Dutch) on the BAREC website.

Guidance on fair compensation of subjects for their participation in clinical research in Belgium

Compensating subjects for their participation in clinical research is currently still a much debated ethical issue. Reimbursing research participants for their study-related expenses is widely agreed as a right, fair and acceptable practice, but compensating them for other reasons, such as for time investment and inconvenience, or for their willingness to participate, is still more controversial.
Overall, guidance documents on this topic from regulatory authorities, research institutions or Human Research Ethics Committees (ECs) are scarce, and only very general in nature.
The ethical controversy on the issue and the absence of detailed guidelines leads to a wide variety of standards and practice, also in Belgium. Therefore, a national initiative providing practical guidance, with broad support of all stakeholders, would be welcome.

The basic ethical principle is that participating in clinical research shouldn't cost the participant anything (on top of standard of care costs, if applicable).

As a general rule, **all study-related expenses** should be reimbursed (when advanced by the participant) or compensated for (when a reasonable fixed lump-sum has been agreed upon). This rule applies to academic as well as commercial studies.

Compensation should be reflected in the ICF (payment form, frequency, amount,...). If the sponsor **does not want to bear study-related expenses**, this should be clearly justified in the application dossier to the EC. If the EC agrees, this should be clearly reflected in the ICF.

Additional compensation, such as for **time investment, inconvenience, or willingness to participate** can be offered, but should be well-justified. If the sponsor **wants to include such compensations**, these should be clearly justified in the application dossier to the EC which evaluates the acceptability of these costs in view of undue influence. If the EC agrees, compensation should be reflected in the ICF (payment form, frequency, amount,...).

Patients or healthy volunteers have equal rights to compensation although expected therapeutic benefit can be factored in.

A study can only take place if the benefit-risk ratio of such study is positive, meaning that the risks for the individual study participant cannot be higher than the potential benefits for such participant or society.

For more information on what are study related expenses or what are considered correct amounts of compensation, please consult the guidance document.

Race and Ethnicity in Clinical Trials with investigational medicinal products

The medical field has undergone significant changes in recent decades, including increased cultural and racial diversification in Europe and the United States due to migration. The number of clinical trials worldwide has also significantly increased, emphasizing the importance of diverse clinical trial populations, in order to optimally reflect the (diversity of) the target population. While clinical trials provide evidence for the efficacy and safety of medical treatments, certain subgroups may not be represented in the trial population, may be disproportionately affected or respond differently to medications. Therefore, it is crucial to have representative study populations that reflect the general population's diversity in terms of age, sex, race, ethnicity, and lifestyle. Currently, there is a lack of diversity in clinical trials, leading to underrepresentation of racial minorities. Adequate reporting of race and ethnicity can potentially contribute to better understanding of cultural, social, and biological differences, enabling the identification of population groups disproportionately affected by certain diseases, along with genetic information collected from study participants. Inclusion of diverse populations in clinical trials not only benefits research accuracy but also promotes fairness and equal care for all patients. Properly informing patients about the collection of sensitive data and addressing barriers, such as mistrust, language and lack of information/access, are important steps in ensuring diverse participation in clinical trials.

Clinical trials/studies considering the collection of race and ethnicity data should provide:

- clear justification for doing so
- detailed plans on how race and/or ethnicity will be defined, measures to promote diversity, how the information will be collected and handled, the option to refuse collection on these data, measures to avoid, identify and address discrimination,…

It is crucial to:

- communicate to participants the importance of voluntarily providing these sensitive data
- ensure that individuals have the freedom to decide whether they wish to share such information

Ethics Committees should verify compliance with these principles in the ICF

For more information on ethical considerations regarding race and ethnicity, please consult the guidance document.

Compensation contraception

BAREC wishes to provide clear guidance on the reimbursement of contraception-related expenses in the context of clinical trials, emphasizing the principle that sponsors should cover these costs when a participant is required to use contraception as part of the study protocol.

The mandatory or recommended use of contraception should generally be regarded as study-related. In line with this perspective, we assert that sponsors are expected to cover the costs associated with obtaining and using contraception methods, ensuring that participants are not burdened with these financial obligations. The study-related contraception should be either reimbursed (if paid in advance by the participant) or compensated for (if a reasonable fixed lump-sum has been agreed upon). This principle is applicable to all clinical research irrespective of the sponsor's nature (commercial or non-commercial) or the type of participants involved (patients or healthy volunteers).

Not meeting these requirements for studies submitted under the framework of CTR/MDR/IVDR, should result in a negative opinion as far as the research ethics committee (REC) is concerned. The purpose of this advice is to contribute to the harmonization of Ethics Committees.

For more information we refer to the BAREC "Guidance on fair compensation of subjects for their participation in clinical research in Belgium".

Trial at a glance

On 3/9/2020, the general assembly of BAREC agrees on the following statement regarding the section "trial at a glance" of the ICF template for interventional clinical trials with IMP on adult patients:

BAREC advises its members to check thoroughly each informed consent form (ICF) and especially the part "Trial at a glance" which must meet all requirements as indicated on the "Model ICF for interventional clinical trials with IMP on adult patients" available on the website of the Clinical Trial College. Not meeting these requirements should result in a negative opinion as far as the research ethics committee (REC) is concerned.

At the Symposium of BAREC on December 9, 2023, an updated decision was reached regarding the 'trial at a glance' section in the ICFs. BAREC agrees that a 'trial at a glance' section is deemed necessary for all ICFs related to adult participants, regardless of the study type and regardless of whether it concerns patients or healthy volunteers.

It is crucial for a participant, who is often not acquainted with the design of studies and the complex terminology related to legal and regulatory aspects, to comprehend the implications of their participation. On the other side, this provides professionals with the advantage of quickly gaining insight into the study.